Doping for Chess Performance

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Abstract

During a chess game, the needed energy is first derived instantly from ATP and creatine-phosphate, then within a few seconds later from glycogen stores in brain, glycogen, muscle and liver and finally, 1-2 hours later from adipose tissue. Anaerobic oxidation of glucose-derivative from glycogen delivers energy 6 times faster than aerobic oxidation of glucose and oxidation of fatty acids; correspondingly, mental activity can perform as well 6 times faster as long as glycogen is available.

The mental profile of chess players correlates with cerebral processes such as attention, conflict solution, memory, motivation and recognition, which together constitute a specific chess-domain expertise.

A chess player may compete best when a) regularly physical exercise is carried out to compete in strenuous chess tournaments and to stimulate mental cognition, b) super compensated glycogen is accumulated in brain, muscle and liver by corresponding nutrition and physical and mental activities, and c. an active mental disposition is available for complex brain tasks during chess by complementary treatment schemes e.g., cogni-tive enhancement (CE) by chess training with chess boards, chess books, building chess images, visual observation of chess games, vocational training with chess, metacognitive training, and additionally regular light physical stress.

An illicit improvement of brain performance for chess playing may be achieved by several measures:

1. Increase of O_2 supply by therapy with erythropoietin (EPO) for chess tournaments at high altitudes and for chess players with lung diseases

2. Increase of body glycogen by therapy with insulin

3. mental stimulation by caffeine

AAS, anabolic agents, amphetamines, nicotine and cocaine have no proven effect on quality of chess playing. Many steroid- and proteohormones such as cortisol, testosterone, ACTH, EPO, GH, hCG, IGF-I, Insulin, LH, present positive effects on brain development and cognition only when present in natural concentrations during development of brain. Pharmaceutical preparations show positive effects only at low baseline cognition. With elevated concentrations, these hormones present negative effects on mental cognition.

Actual CE drugs have effects only with persons at low cognitive baseline. With normal persons, CE is still below clinical significance.

Regular non-medical use of steroid and proteohormones in elevated concentrations and CE-drugs must also consider numerous side effects ranging from simple metabolic disturbances through cardiac problems to cognitive decline to tumorgenesis and sudden death.

Keywords: Chess; Doping

Introduction

Chess is officially recognized as sport by the IOC. Several national chess organizations however, such as the DSB (German Chess Organization) in Germany and the Chess Federation of Canada fall outside sport organizations for funding and are therefore practically excluded from official financial support [1]. In order to obtain and thereafter maintain that recognition as sport the DSB has to adopt the national as well as the Olympic anti-doping policy.

Doping is an area of ongoing public, legal, and medical debate and in recent years it has been reported to be connected with many sports including athletics, cycling, body building, soccer, swimming [2] and recently also with chess [3]. According to Dekhuijzen [2] there are five prohibited classes of substances: stimulants, narcotics, anabolic agents, diuretics, and peptide and glycoprotein hormones and their analogues. Doping classes should be classified preferably by desired effects on energy availability, muscle performance, respiratory and renal system and mental performance.

The first chess-doping scandal happened on the last day of the Chess Olympiad in November 2008 in Dresden. Who knows what was going through Iwanchuk's head (actually 4th on world chess ranking list 2014), when on Nov. 25 in Dresden, the last day of the Chess Olympiad, a judge asked Iwanchuk to submit to a drug test. Iwanchuck stormed out of the room in the conference center, kicked a concrete pillar in the lobby, pounded a countertop in the cafeteria with his fists and then vanished into the locker-room [3].

Especially in chess, doping tests are usually characterized as a joke, a waste of time and money.

Are doping tests justified for chess players?

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Metabolic and Mental Requirements for Doping in Chess

When a competitive chess player considers to increase physical and mental disposition for successful chess playing performance before a chess competition, which of the body functions should be increased?

Chess players need for successful professional chess competitions

Physical endurance instead of maximal physical performance for chess tournaments lasting for days or weeks: Physical exercise should be carried out on the oxidative level to strengthen the cardio-respiratory system [4,5] and prepare the brain to respond to cognitive stimulation [6]. A cognitive training then induces neuronal changes in specific networks associated with the trained skill.

Oxygen (O_2) needed for brain energy derived from ATP coming from glucose, glycogen and fat metabolism: O_2 is taken up by lungs and transported to cells via the erythrocytes (Ery). The O_2-concentration in the Ery is usually expressed as oxygen saturation, which is found in arterial blood between 94-98% and in venous blood between 80-85%. It can be measured by blood-gas analyzers. During physical exercise, O_2 is taken up from Ery by muscle cells to produce energy. At the same time, new O_2 enters the body by the lungs. In strenuous exercises with a heavy workload, O_2-consumption in muscle cells exceeds O_2-uptake by lungs and O_2-saturation in Ery consequently decreases [7]. Since the physical workload during a chess game or a chess tournament is normally within O_2-balance, a decrease of O_2-saturation in Ery will happen most unlikely.

Replenished glycogen-stores in brain, liver and muscle: The adult brain relies on glucose for its energy needs and stores it in the form of glycogen, primarily in astrocytes. Animal and cell-culture studies indicate that brain glycogen supports neuronal function when the glucose supply from blood is inadequate or during neuronal activation [8]. Human brain glycogen content is estimated at ~3.5 μmol/g, i.e., three- to fourfold higher than free glucose at euglycemia [9].

While availability of fat in humans is relatively constant, ATP, creatine-phosphate (CP), glucose and glycogen stores in humans change rapidly during physical and mental strain. During mental exercise such as chess as well as physical exercise, energy is used according to availability with respect to delay time, velocity of resynthesis and total quantity. The corresponding data are listed in (Table 1).

Amounts of substrate available, delay time of production and maximal rates of production in a 70kg man (estimated muscle mass 28 kg), in parts completed and normalized. Glycogen and glycogen metabolism in brain were calculated from brain weight [12] and glycogen content in brain [9].

In addition to the primary availability of human energy resources (Table 1), production of glycogen from glucose is also a rapid process starting at the beginning of glycogen use by mental and physical activity. Glycogen is resynthesised within 40 minutes [13].

It becomes clear from these data, that energy production from glycogenolysis necessary for mental or physical work delivers ATP within 5-10 seconds, in contrast to energy from fatty acids in more than 5000 seconds. In addition, glycogen is continuously and rapidly resynthesised as long as glucose is available. Secondly, rate of ATP-production from anaerobic glycolysis is at least 6times faster than from oxidation of fatty acids and 3times faster than oxidation of glucose.

In conclusion, mental activity during chess games or physical exercise can only function at highest performance when glycogen is still present in sufficient amounts. When glycogen stores are expended, brain "talks" to adipose tissue [14], which then delivers energy from fatty acid oxidation. Mental and physical performance speed decreases now and mental and physical performance declines cumulatively and finally fatigue occurs.

Active mental disposition for complex brain tasks during chess: Chess players have no exceptional intellectual abilities. Chess expertise can be best predicted by a domain specific practice.

CE for chess playing and of course for mental performance in physical sport in a natural setting can also be achieved by numerous natural molecules present in humans, such as insulin, growth-hormone (GH), Insulin-like-growth factor-1 (IGF-1), testosterone and estradiol. Especially diabetic persons are at the receiving end of insulin deficiency concerning mental disposition [15].

Many of these molecules are also available for medical therapy but also for unethical use to achieve improved mental and athletic performance.

In addition to natural proteo and steroid hormones numerous drugs have been synthesised with the aim, to enhance cognition for medical therapy of brain disabilities, such as narcolepsy, dementia, Alzheimer's disease (AD), Parkinsons disease (PD), schizophrenia or attention deficit hyperactivity disorder (ADHD) and depression [16].

Substances Suited for Doping in Chess

Androgenic Anabolic Substances (AAS)

Natural steroids: Mother substance to all natural steroid hormones, such as testosterone, estradiol, cortisol and aldosterone, is cholesterol. On the metabolic pathway from cholesterol to the gonadal and adrenal hormones, numerous steroid metabolites such as dehydro-epi-androsterone-sulfate (DHEAS) appear. In addition, Testosterone is further metabolized by enzymatic reactions, so that many steroid metabolites appear in the human body, which present all or only part of the properties of testosterone (26 in the WADA-List from 2014). In addition, testosterone analogues are synthesized by chemical reactions (44 in the WADA-list from 2014), which are not present in the human body, but have all or only some properties of testosterone.

In this work, the author concentrates therefore on the effects of

Energy Derived from	Maximal Rate of ATP Synthesis (mmol ATP/min)	Delay Time	Amount Available (mol)
Fatty acids→CO_2	0.4	> 2h	4000
Glucose from blood → lactate	2.35	approx. 90 min	0.11
Muscle glycogen→lactate	2.35	5-10 sec	6.7
Muscle glycogen →CO_2	0.85-1.14	several min	84
Liver glycogen→CO_2	0.37	several min	19
Brain glycogen→lactate	2.35	5-10 sec	0.5
Glycolysis→lactate	2.35	5-10 sec	6.7
ATP, CP→ADP, creatine	4.4	instantly	0.67
	[10]	[11]	[10]

Table 1: Availability of human energy resources.

testosterone on human chess performance.

Bilalic and Chabris found no gender-specific chess excellence [17-19]. Since men and women may be differentiated mainly by their testosterone and not estradiol concentration (Table 2) [20], testosterone in physiological concentrations should therefore have no effect on mental chess excellence.

Hormone-values decrease from peak values by ca. 1% per year in women [21] and men [22].

When applying supra-pysiological androgens (for example nandrolone, glycogen in heart, liver and muscle remain unchanged [23] and competitive behaviour is increased in rats [24] and primates [25]. Moreover, this behavioural response was further increased when the androgens were combined with the stimulant amphetamine [26]. In addition Mazur [27] observed that winners of chess tournaments have higher testosterone concentrations than losers. Also, in certain circumstances, chess competitors show rises in testosterone-concentration before their games, as if in preparation for the contests.

The positive role of androgens on brain cognition and aging are well known [28]. Androgen deficits cause significant loss of synapses in the hippocampus in rodent and nonhuman primates, increases amyloid deposition in human and rodent models and causes changes in neurotransmission in prefrontal cortex in rodent models [28]. Recent work suggests that these changes modify age-related cognitive loss, particularly to memory in men. However, testosterone treatment of healthy older men without cognitive deficits improved also cognitive properties, for example memory [29].

In the work of Davison [30] a comprehensive summary of testosterone effects on brain in men and women is found: neuroprotective properties, better performance in tasks of mathematical and spatial ability, superior performance on verbal fluency and memory tasks.

Is testosterone related to competition among women as it is among men? Is hormonal mediation of competition primarily a male characteristic [27]?

Possibly women have more sensitive testosterone mechanisms, so the smaller amount of the hormone found in women is sufficient to produce comparable effects.

Alternatively, estrogens or other hormones [31], that are more prevalent in women than in men may play an analogous role to that of testosterone. There exists some evidence to this suggestion. Azcoitia [32] observed that some of these effects of testosterone are blocked by aromatase inhibition and thus appear to be estrogen mediated. Aromatase is the enzyme responsible for the conversion of testosterone to estradiol. Janowsky [28] nreported that the conversion of testosterone to estradiol may play a special role in women in the preservation of memory in aging. In addition, estradiol enhances hippocampal dependent learning and memory in aged male and female mice [33].

The downside of AAS

Long-term use of supra-physiologic doses of AAS may cause irreversible cardiovascular toxicity, especially atherosclerotic effects and cardiomyopathy. In other organ systems, evidence of persistent toxicity is more modest. High concentrations of AAS, comparable to

those likely sustained by many AAS abusers, produce apoptotic effects on various cell types, including neuronal cells-raising the specter of possibly irreversible neuropsychiatric toxicity [34].

Long-term AAS users showed no significant differences from nonusers on measures of response speed, sustained attention, and verbal memory. Concerning visuospatial memory, however, AAS users performed significantly more poorly than nonusers, and within the user group, visuospatial performance showed a significant negative correlation with total lifetime AAS dose. These were large effects on pattern recognition and Memory. Long-term AAS users underperformed nonusers by almost one standard deviation and performance on this test declined markedly with increasing lifetime AAS dose [35].

According to Grönbladh [36] the AAS analogue ND induced impairments of memory and also altered specific receptors in brain necessary for GH and IGF-I-activity. Furthermore, ND lowered IGF-1 plasma concentrations. The findings regarding ND are worrying considering the common use of AAS among adolescents.

Conclusion: Long-term AAS use has no direct effect on energy for mental cognition and level of cognition. Concerning its effect on GH and IGF-I, visoaspatial memory and pattern recognition memory will be affected indirectly. AAS-users will perform mentally significantly worse than non-AAS-users.

Anabolic Agents (AA) ($ß_2$-adrenergic drugs, no steroids): $ß_2$-Adrenergic drugs (clenbuterol for example) have anabolic effects, induce skeletal hypertrophy, and are found in brain after application. Clenbuterol has no effect on glycogen content in cells (absence of DNA-increase) [37].

Clenbuterol and other ß2-agonists as anabolic drugs have no effect on GH- or thyroid and insulin-stimulation [38]. They rather act through increasing RNA and protein-synthesis. In summary, anabolic agents are able to increase skeletal muscle force production only when administered in supra-physiological doses or in combination with excessive training [2].

Clenbuterol improved performance in many young and aged rats and monkeys who performed poorly under control conditions. The effects of clenbuterol were not universal and depended on the cognitive status of the animal: the drug moderately improved only a subset of animals with working memory impairment [39].

In overdoses, Clenbuterol causes cardiac toxicity and type II myocardial infarction (MI) with associated symptoms such as agitation, palpitations, tachycardia, hypokalemia, and hyperglycemia [40].

Conclusion: In conclusion, men and women both have their specific hormonal endowments to participate sufficiently in competitive chess. Therapeutic treatment with testosterone or estradiol in age-dependent decrease of gonadal hormones or in endocrine defects in the hypothalamus-hypophysis-gonads axis will improve cognitive performance as well as testosterone abuse by healthy older men and women. Longer use of supraphysiologic AAS concentrations, however results in severe clinical atherosclerotic effects, cardiomyopathy and apoptotic effects on neuronal cells. The latter side effects cause a significant decline of visuospatial performance and pattern recognition. The presented clinical data show that AAS use in a natural setting of gonadal hormonal endowment will impair chess performance.

Energy for Chess Performance

Oxygen [O_2]

Specimen serum	Testosterone nmol/l	Estradiol pmol/l
Male	10-42	37-110
Female (day 1-10 menstrual cycle)	0.7-2.6	50-100

Table 2: Reference values of testosterone and estradiol in adult men and women.

In general, the respiratory system does not limit maximal oxygen consumption in healthy subjects. Only in highly trained endurance athletes may blood oxygen saturation fall during heavy exercise [2]. Troubat [14] observed in his study a constant ventilation rate, so that a limitation of O_2 during mental activity was excluded.

A limitation of the study of Troubat [14] remains because of the relative short time of the game (on the average 45 minutes for each player). In blitz-chess tournaments for example, the players have only 5 minutes for the complete game so that 10times as many conflict situations must be solved per time unit. In addition, Hollinsky [4] described, that HR measured during a chess tournament included peaks in excess of 220/min and a single maximum of 223/min. Not surprisingly, at least to chess players, the peak HR is reached in the time pressure phase towards the end of the sixth hour of play [4,41]. It is also interesting to note that this player's adrenaline level reached almost eight times his normal rate, while Pfleger [41,42] observed increases of more than 3fold. Hollinsky [4] noted that subjects experiencing HR in excess of 200/min and big increases in catecholamines were prone to make more simple mistakes on the chessboard because they were under extreme physical pressure.

Conclusion: A beneficial effect of drugs increasing availability of O_2 for the chess player cannot be completely excluded, therefore, especially for chess-players with lung diseases, such as cystic fibrosis [43], or during chess plays carried out at high altitude [44].

Glycogen

In terms of rapidly available energy from glucose and glycogen, only a limited amount necessary for the completion of most of the competitions of chess players can be delivered [14,45]. The continuation of competition must then be carried out with energy derived from adipose tissue at a slower rate of availability. The high rate of mental performance is thus impaired and must be reduced. Especially attention and conflict control are involved [46,47].

Two natural methods are available to increase glycogen content in the body in order to increase the rapidly available energy.

Glycogen supercompensation is one of the adaptations induced by physical training. This happens when glycogen recovers to above its basal level after it decreases with acute exercise. Greater glycogen depletion induces greater glycogen supercompensation in skeletal muscle [48], suggesting muscle glycogen supercompensation is inducible in more active muscle for metabolic adaptation.

Exercise also increases neuronal activity and creates an energy demand in the brain [49,50]. During the recovery phase after exhaustive exercise, glycogen supercompensation in the brain occurs earlier (6h) than that of skeletal muscles and liver (24h). Brain glycogen levels decreased by 50–64% with exhaustive exercise, and supercompensated by 29-63% (whole brain 46%, cortex 60%, hippocampus 33%, hypothalamus 29%, cerebellum 63% and brainstem 49%) at 6 h after exercise [51]. It must be assumed, that total body glucose energy resources (i.e. glycogen and free glucose) are interconnected by the central blood-glucose, which serves as a common regulating variable. Peters formulated his 'Selfish Brain Theory' regarding competition for glycogen energy resources throughout the whole body [52]. However, evolution would only support a cooperation rather than a competition of body organs for energy resources. In addition, restoration and supercompensation of brain glycogen after physical exercise is preferably accomplished if compared to muscle glycogen [51].

Additionally, 3 days of a hyper-carbohydrate diet seems to increases

basal levels of muscle glycogen (also known as 'muscle glycogen loading'), and prolongs the time required to exercise exhaustion [53].

To potentiate glycogen synthesis under natural conditions, many athletes use supraphysiologic doses of anabolic androgenic steroids (AAS). However, Cunha [23] could show, that administration of superphysiological doses of ND had no effect on heart, liver and muscle glycogen of male rats.

Conclusion: In order to extend availability of rapid energy necessary for intensive chess playing, the chess player can increase his glycogen stores in brain, liver and muscle through regular aerobic and mental exercise as well as through carbohydrate-rich nutrition before the competition. Physical exercise also supercompensates glycogen of brain regions involved in mental exercise such as chess.

AAS have no effect on glycogen content of man.

Stimulants

Amphetamines: Amphetamines stimulate CNS, increase arousal, medullary respiratory center [2] and may mask fatigue by increase of free fatty acids [54].

It is hypothesised that these drugs may enhance all types of performance [55]. Tikhomirov [56] postulated, that the heuristic character of chess players can be explained by a complex interaction of emotional, motivational and cognitive processes and showed, that low arousal is associated with failure to solve the more difficult chess problems. Gobet [57] defines emotions as adaptive, quick and efficient alert systems. Emotions are important in acquiring and maintaining expertise.

In general, the data on acute effects show that amphetamines might improve cognitive performance in selected domains, that is, visuospatial perception, attention, and inhibition.

With the exception of the severe clinical side effects of amphetamine treatment, the clinical significance of these findings may be limited because cognitive functioning overwhelmingly falls within the normal range when compared against normative data.

Regarding long-term effects on cognitive performance and brain-imaging measures, statistically significant differences between methamphetamine users and control participants have been observed on a minority of measures [58]. Despite the lack of enhancement observed for most measures and most participants, participants nevertheless believed their performance was more enhanced by the active capsule than by placebo [59].

Another frequently reported deleterious effect associated with amphetamine abuse and dependence is cognitive impairment. Unlike the scant literature examining the effects of the drug on dental health, there is a burgeoning amount of information detailing the impact of methamphetamine on cognitive functioning. The dominant view is that illicit methamphetamine use causes a broad range of cognitive impairments [60]. In addition, Methamphetamine abuse is associated with multiple deleterious medical consequences, including paranoia mimicking full-blown psychosis [61] and hypertensive crisis leading to stroke [62].

Conclusion: Clinical data show, that acute amphetamine use has no effect and abuse will impair cognitive and chess performance.

Caffeine: Caffeine is the world's most widely consumed psychoactive substance, with 74 percent of Germans drinking several times daily [63]. The IOC classified caffeine as a doping agent in 1962,

removed it from the list of banned substances in 1972, and currently has classified it as a restricted drug (positive at >12 mg/ml in urine [2], in 2014 Included in WADA 2013 Monitoring Program and relevant for in-competition testing only.

Caffeine initially stimulates the CNS at the level of the cerebral cortex and medulla and only later stimulates the spinal cord (at higher doses). Its effects begin within 1h and last for 3-4h. Caffeine significantly inhibited response blocking (attention lapses) in car drivers [64]. Caffeine elevates mood [65], increases alertness, reduces fatigue by lowering the threshold for exercise-induced β-endorphin release. An increase in β-endorphin is well known to enhance exercise performance through its ability to decrease pain perception and promote euphoria [66] and this not so much by sparing glycogen as usually is presumed [2,67].

Normal caffeine consumption improves performance on tasks that require alertness, such as simulated driving tasks. The effect on more complex cognitive tasks is less clear, although there is evidence to suggest that high consumption is associated with better performance, especially in older people [68].

Elevated caffeine: Caffeine intakes of ≥ 1.4 mg/kg increased aortic stiffness, increased vascular resistance, decreased cerebral blood flow, and increased plasma epinephrine, lipids, and renin activity. The effects were typically greater in low users and in older subjects than in habitual caffeine consumers, and were exacerbated by concurrent hypertension. Caffeine increased plasma homocysteine levels in most experimental and population studies where it was evaluated. Epidemiological studies provided inconsistent association of caffeine with blood pressure in children. All but one of the 14 case-control studies with adults found a positive association of caffeine intake with increased risk of cardiotoxicity, including MI and sudden cardiac death with 12 g of pure anhydrous caffeine [69]. The cohort prospective studies, however, provided conflicting results, some finding an elevated risk of MI, increased blood pressure, or coronary death from consumption of 6-19 mg/kg/day, but other studies finding no association or an inverse association. Due to the heterogeneity of the data, a lowest-observable adverse effect level cannot be reliably determined for the effect of caffeine on cardiovascular parameters [70], although a research review regarding caffeine consumption concluded that among the healthy adult population a moderate daily caffeine intake of ≤ 400 mg (on the average 4 pots of coffee) was not associated with any adverse effects [71].

Conclusion: Caffeine can be characterized as a stimulant for improving chess playing with respect to stimulation of cerebral cortex, increasing alertness, reducing pain perception and promote euphoria and mood.

Diuresis

In addition, caffeine may be characterized as a diuretic agent [72] (see diuretics).

Nicotine: Nicotine is a highly addictive substance, and cigarette smoking is a major cause of premature death among humans. Little is known about the neuropharmacology and sites of action of nicotine in the human brain.

Intravenous nicotine strongly activates in humans a distributed system of CNS regions implicated in the control and regulation of many of the behavioral states long attributed to nicotine use. The cingulate and several frontal lobe divisions, including the dorsolateral, orbital, and medial frontal, were among the most prominently activated regions

[73]. The frontal lobes-with their rich dopamine innervation-and the cingulated cortex-through its connections with many neocortical association, motor, and sensory regions-have been thought to be involved in the processing of such diverse cognitive states as working memory, attention, motivation, mood, and emotion [74].

Studies of the effects of nicotinic systems and/or nicotinic receptor stimulation in pathological disease states such as AD, PD, ADHD and schizophrenia show the potential for therapeutic utility of nicotinic drugs.

In contrast to studies in pathological states, studies of nicotine in normal-non-smokers and in normal elderly people tend to show deleterious effects [75], while nicotine had no effect in young persons. The effect of nicotine was dependent on baseline cognitive performance in young and old people with subjects with lower performance baseline benefiting from nicotine administration, while those with higher baseline performance performed worse after nicotine administration [75].

Although normal individuals are unlikely to show cognitive benefits after nicotinic stimulation except under extreme task conditions, individuals with a variety of disease states can benefit from nicotinic drugs. Attentional function/dysfunction may serve as an endophenotypic therapeutic target for nicotinic drug development [76].

Elevated nicotine: Though nicotine is one of the most toxic drugs of abuse, it has rarely led to fatalities. Sudden death can be caused by cardiovascular arrest, respiratory muscle paralysis and/or central respiratory failure. One fatal case was reported in the scientific literature [77]: A 42-year-old man was found dead by his wife. He was lying on the floor, next to a box containing many empty bottles of beer and vodka. Some labelled chemical bottles found at the scene contained various substances, including nicotine and brucine. Gross examination of the organs at autopsy revealed no specific findings. The toxicological examination failed to disclose any lethal toxic agents other than a high concentration of nicotine and its primary metabolite cotinine in femoral venous blood (2.2μg/mL). Blood alcohol was determined to be 2.1 g/L in femoral venous blood.

Conclusion: Chess players will not benefit from nicotine; on the contrary, at least elderly chess players might perform worse after nicotine administration.

Narcotics

As an example, cocaine will be discussed. The few studies on cocaine and exercise suggest that little to no performance gains are incurred from cocaine use. Moreover, the sense of euphoria may provide the illusion of better performance when, in actuality, performance was not improved or was impaired [55].

Cocaine abuse: Cocaine is a potent sympathomimetic drug that is associated with cardiotoxicity, including ventricular arrhythmia, systemic hypertension, acute MI and left ventricular hypertrophy. associated with a significant degree of cardiotoxicity, particularly coronary artery disease and ventricular hypertrophy, independent of cocaine concentration [78]. According to Degenhart [79] mortality is four to eight times higher among cocaine users than age and sex peers in the general population.

Cocaine has a negative impact on exercise endurance [80].

Conclusion: Beneficial effects of narcotics on chess excellence have not been observed.

Diuretics

Diuretics would impair verification of substances in blood, which ameliorate chess performance. Caffeine shows diuretic properties (see chapter stimulants).

Peptides and proteohormones (EPO, GH, IGF-1, hCG, LH, Insulin, ACTH, Cortisol).

Erythropoietin (Epo)

Biologic effects: Epo is a naturally occurring glycoprotein that stimulates the proliferation and differentiation of erythroid progenitor cells [81].

Elevated concentrations: In elevated concentrations, Epo causes numerous, serious and often lethal side effects. Among these are for example in brain cerebral seizures, hematomas and haemorrhages [81] and stroke, hypertension, and cardiovascular risks vascular access, thrombosis risks [82]. In the clinical trial of Bennett [82] more than 90% of the participants reported adverse events. More than 10% discontinued the test, ca. 10% died during the test.

Conclusions: Epo has no effect on chess performance with the exception of chess plays at high altitudes and persons with lung diseases (see chapter O_2).

Growth hormone (GH)

Metabolic effects: The metabolic effects of GH are listed here according to Vijayakumar [83] and Møller [84]:

- Stimulation of lipolysis in the adipose tissue resulting in an increased flux of free fatty acids (FFAs) into the circulation, muscle and liver.

- Stimulation of triglyceride uptake and subsequent storage.

- Antagonism of insulin action.

- Net anabolic effect on protein metabolism, may be due to fluid retention rather than muscle hypertrophy [85].

- Decrease of glucose oxidation (secondary to an increase in lipid oxidation) and suppression of muscle uptake of glucose.

- With abuse or therapeutic excess, GH shows diabetogenic actions with hyperinsulinemia, which may in the long term induce increased cardiovascular morbidity and mortality.

Furthermore, GH has a net anabolic effect on protein metabolism although the molecular mechanisms of its actions are not completely understood.

Athletic performance: GH is reportedly used to enhance athletic performance, although its safety and efficacy for this purpose are poorly understood. In a thorough meta-analysis of GH misuse in physical exercise, Liu [85] used 27 studies published in 44 articles to evaluate the efficacy of GH on athletic performance. The authors conclude: Claims that growth hormone enhances physical performance are not supported by the scientific literature. Although the limited available evidence suggests that growth hormone increases lean body mass, it may not improve strength; in addition, it may worsen exercise capacity and increase adverse effects.

The only study found in Medline with positive effects of GH on physical performance of recreational athletes was published in by Meinhardt [86].

Brain: One aspect of GH properties has not been considered in the discussion of human performance: the effects of GH on brain development (see also IGF).

The CNS is a target for GH indicating that the hormone crosses the blood–brain barrier.

GH-receptors are present in many regions of the brain [87]. Among these are in humans as well as in rats the choroid plexus, hippocampus, hypothalmus, and spinal cord.

GH (together with IGF-1) induced in the hypophysectomised rat cellular proliferation by a factor of more than 2fold in the dentate gyrus (part of hippocampus, location of memory, short conflict control), hippocampus (memory, conflict control), corpus callosum (brain structure to connect actively both brain halves), striatum (regulation of voluntary motor activity) , and the parietal (reception and processing of sensory information from the body) and piriform cortices (motivation, processing of information) [88].

The hippocampus, for example, is involved in GH dependent action on memory and cognitive function [89].

GH replacement therapy was found to improve the psychological capabilities in adult GH deficient (GHD) patients. Furthermore, beneficial effects of the hormone on certain functions, including memory, mental alertness, motivation, and working capacity, have been reported [89]. Falleti [90] evaluated 13 selected studies concerned with the effects of GH deficiency and GH replacement on cognitive performance in adults. In conclusion, this meta-analysis clearly demonstrated that initially present poor cognitive performance can be ameliorated with GH treatment. GH treatment also improved in man several cognition tests including Intelligence-, information-processing-learning-tests after traumatic brain injury [91].

GH in a natural setting, however, has another surprising effect. Mice lacking GH or GH receptor outlive their normal siblings and exhibit symptoms of delayed aging associated with improved insulin signalling and increased stress resistance. Recent studies of the role of the somatotropic axis, and specifically GH, in the control of aging and longevity have added new evidence for the anti-aging and life-extending effects on GH resistance and GH deficiency in laboratory mice [92].

Elevated GH: Elevated GH concentrations, that occur for example in acromegaly, cause insulin resistance, leading to hyperglycemia, hyperinsulinemia, decreased glucose utilization, increased lipoplysis [93], central hypothyroidism [94], leukemia in cell culture [95]. Very disturbing data were represented by Takala [96]: two parallel studies provided strong evidence, that the administration of high doses of GH to critically ill adults receiving prolonged intensive care is associated with an increase in mortality; among the patients who survived, the duration of mechanical ventilation, intensive care, and hospitalization was prolonged by GH. GH therapy can have fatal consequences.

Persons with acromegaly, a syndrome that results when the anterior pituitary gland produces excess GH, showed cognitive and neurophysiological impairment, characterized by moderate-to-severe memory impairment and decreased neural activity in specific brain areas [92].

Conclusions: The presented data do not indicate that GH might improve mental performance by means of energy availability.

When the effects of GH on brain performance in a natural setting are considered, a definite improvement of mental performance such as memory, learning, conflict control can be achieved by GH treatment of

GH-deficient persons.

Chronic elevated GH will result in poorer cognitive performance.

Insulin-like Growth Factor (IGF-I)

IGF is a naturally occurring single chain polypeptide which has 48% structural homology with pro-Insulin. Insulin, GH and nutrition are the main regulators of hepatic IGF-production [97].

Glucose: IGF-I has an insulin-like activity, i.e. increased glucose disposal and suppressed insulin secretion [97].

Protein: Russel-Jones [98] could show, that IGF-I induced protein synthesis, but had no effect on protein degradation, while insulin reduced protein degradation with no effect on protein synthesis.

Brain: The concept that GH and IGF-1 are required for normal development of the mammalian body and, more recently the brain is supported by a vast experimental literature. Aleman [99] observed, that circulating IGF-I plays an ameliorating role in the age-related reduction of certain cognitive functions, specifically speed of information processing. IGF-1 and GH cross the blood–brain barrier and are bound by binding sites for example in the hippocampus, a brain structure important in the maintenance of cognitive functions such as learning and memory [100]. In recent years, much attention has focused on age-related decreases in serum GH and IGF-1 as potential mechanisms that may influence cognitive function in the elderly. In rodents, GH and IGF increase cell genesis in several regions of the brains of GH-IGF-I-deficient hypophysectomized rats [88] and long-term GH/IGF-1 replacement improves learning and memory in aged rats. While the exact mechanism underlying these cognitive improvements is unknown, GH and IGF-1 replacement to aged animals increases neurogenesis, vascular density, glucose utilization, and alters NMDA receptor subunit composition in brain areas that are implicated in learning and memory [101]. Based on the available data, GH or IGF deficiency could contribute to the deterioration of cognitive functions observed in the elderly [100].

Many new functions of IGF-I in the brain and elsewhere are arising. This peptide forms an intricate functional network with other members of the family, in particular with insulin and GH, and interacts with many other neurotrophic signals. All brain cells are modulated by IGF-I, and its key role in health and disease is now firmly established. Whether IGF-I constitutes a master regulator of brain homeostasis is open to discussion, but current knowledge of its functions in this organ support this possibility [102].

Elevated IGF-I: In elevated concentrations, IGF-I is both an anabolic and mitogenic agent for skeletal muscle or muscle lineage cells [103]. High concentrations of IGF-I were also associated with an increased risk of prostate cancer and premenopausal breast cancer [104]. Results from recent studies provide evidence of cognitive and neurophysiological impairment, characterized by moderate-to-severe memory impairment and decreased neural activity in specific brain areas. High levels of IGF-I in acromegaly patients could be the basis for these findings [92].

Conclusion: In conclusion, IGF-I improves in natural concentrations energy availability as well as cognitive function in man. In chronic elevated concentrations IGF-I causes moderate to severe cognitive impairment.

Luteotropic hormone (prolactin, LH) and human choriogonadotropin (HCG)

Gonads: Parenteral administration of LH or HCG stimulates the production of testosterone in the testes of males and progesterone and estradiol in females and these gonadotropins can therefore be used by athletes to enhance muscle strength [105]. However, they are more expensive and less efficient than testosterone and anabolic steroids. Therefore their main use is probably to stimulate gonadal testosterone production during and after self-administration of testosterone or anabolic steroids. A positive effect of HCG on muscle strength has not been demonstrated in women and elevated concentrations of HCG in females are often caused by pregnancy. The use of gonadotropins is therefore prohibited only in males but not in females [106].

Brain: One of the processes associated with age-related reduction of testosterone concentration in men [107] and estradiol in women [108] is the cognitive decline in men [109] and women [108].

Declining levels of estrogen in women [108] result in increases in gonadotropins such as LH and HCG through loss of feedback inhibition. These processes are considered to be crucial for the development of age-related cognitive impairments and even the progression of AD [110]. The question arises, whether the loss of estrogens or the high levels of gondadotropins are the cause for the cognition decline.

HCG and LH are capable to cross the blood-brain barrier and can be detected in cerebrospinal fluid and in several parts of the brain. Receptors for gonadotropins are found in the hippocampus [111,112], a key brain area responsible for cognition affected by aging and which is severely deteriorated in AD [113].

Bryan [110] could indeed show, that restoration of cognitive impairments is possible in laboratory animals (mice) by downregulation of gonadotropins without use of estrogens. Similar results were published by Casadesus [114], which showed that transgenic mice with overexpressed LH showed decreased mental performance. These findings indicate that increased luteinizing hormone levels, in the presence of functional receptors may be responsible for cognitive decline after menopause.

Berry [115] tested female rats for spatial memory of rats after treatment with HCG and observed a decline of memory performance.

Elevated LH: Elevated LH is usually associated with hypogonadism, low testosterone and normal FSH blood levels. hCG administration rises plasma testosterone and normalizes the clinical condition [116]. Cognitive impairement in central hypogonadism in male is usually associated with pituitary tumors [117].

Conclusions: Gonadotropins HCG and LH show two-edged effects on brain performance, i.e. a decline by the gonadotropins and a rise caused by induced testosterone.

Insulin

Almost all cell types are responsive to insulin. However, brain, liver, muscle, and adipose tissue are the most sensitive to the hormone, rendering it the most important anabolic hormone identified to date. The major effects of insulin are manifold, but may be categorized for four main purposes to enable synthesis of carbohydrates, fat and proteins and prevent neurodegeneration [118,119]:

Glucose: Insulin increases glucose transport across the cell membrane in adipose tissue and muscle. It accelerates glycolysis in muscle and adipose tissue depending on phosphorylation of glucose. Insulin increases of glycogen synthesis in adipose tissue, muscle, and liver. It decreases glycogen breakdown in muscle and liver and rate of glycogenolysis and gluconeogenesis in liver.

Lipids: Decrease of rate of lipolysis in adipose tissue resulting in a decrease of blood fatty acid concentrations. Insulin accelerates synthesis of fatty acids and neutral fat molecules, and increases the rate of cholesterol synthesis in liver.

Protein: Increase of transport of some amino acids into tissues and rate of protein synthesis in muscle, adipose tissue, liver, and other tissues. Insulin decreases rate of protein degradation in muscle and urea formation.

Brain: In brain insulin regulates both peripheral and central glucose metabolism and is therefore associated with neuroprotective properties. Insulin signalling in brain is positively associated with learning, memory, and negatively with age related neurodegenerative diseases. Insulin resistance in brain has also been associated with diabetes and aging in CNS with AD considered to be the "brain-type diabetes" [119].

Insulin application: Insulin is available for therapeutic therapy of insulin deficiency in numerous formulations. Its use by the intramuscular or subcutaneous route however is often associated with non-adequate concentrations in blood.

The development of technologies in the last decade has brought non-injectable insulin delivery to reality. A rigorous research effort has been undertaken worldwide to replace the authentic subcutaneous route by a more accurate and non-invasive route. Peroral, nasal, and pulmonary administration has demonstrated good potential for treatment of diabetes. In addition, transmucosal, buccal, ocular, rectal, and vaginal routes of insulin have also shown to decrease serum glucose concentrations. The transdermal route using various technologies also exhibits success in delivering insulin [120]. These new application methods seem to favour non-authorized application of insulin, since a hypoglycaemia will not rise as easily as with insulin injection; additionally, insulin determination in blood and urine will be complicated because insulin may not be metabolized by the circulation route.

Elevated insulin: The administration of exogenous insulin by various routes increases muscle glycogen before and after the recovery stages of strenuous exercise. This may improve mental and physical performance with the rapidly available energy and may assist in recovery of mental and physical exercise.

Beside diabetic persons, hypoglycaemia is a regular occurrence in people, who inject insulin to improve athletic performance and may be associated with cognitive and affective outcomes [121]. Mood changes by changes by fluctuations in glycemic control together with depressive and anxiety states, sometimes also with euphoria. The most serious consequences of hypoglycaemia is a decrease of brain glycogen, together with hypoglycaemic convulsions, neuro-glycopenic coma [122] and even death due to brain failure [123].

Conclusions: Insulin is responsible for the transport of glucose through cell membranes to glycogen synthesis, and then to glycogenolysis and glucose-1-phosphate in all organs of the human body which contain glycogen. Insulin is therefore essential for the function of energy metabolism depending on glucose. It therefore has neuroprotective properties and insulin is signalling for a positive effect on learning and memory and a negative effect on age related neurodegenerative diseases. Insulin therefore would definitely improve conflict control during chess playing.

Adreno-Corticotrophic Hormone (ACTH) and corticosteroids (cortisol)

Adrenocorticotrophic hormone (ACTH), also known as corticotrophin, is a proteohormone and secreted by the hypophysis. It is produced on the basis of an diurnal rhythm with high values in the morning and low values around midnight and often by mental and physical stress via the hypothalamic-hypophysis-axis. Its principal effects are increased production and release of corticosteroids. The principal steroid hormone produced by the adrenal gland is cortisol, which also is present in blood following the diurnal rhythm of ACTH.

ACTH has been used therapeutically in some childhood seizures. During longer ACTH-treatment, brain (rat) develops more dendrite branches [124]. Some additional effects of ACTH have been described on neurotransmitters dopamine, norepinephrine, serotonon and GABA (gamma-aminobutyric acid) [125]. Therapeutic cortisol or analogues are used for diagnosis of Morbus Cushing or Addison and for control of inflammation diseases.

Conclusions: The benefits and disadvantages of ACTH on performance enhancement in physical and mental strain therefore will be mainly derived from cortisol and analogues.

Glucocorticoids (Cortisol and Analogues)

Glucose

In the fasting state and in physical or mental stress, cortisol accelerates gluconeo-genesis i.e. synthesis of glucose from glucogenic amino acids [126] in brain, liver, and muscle-cells and stimulates anti-inflammatory reactions. In addition, cortisol induces glygogenolysis in liver, brain and muscle [127] by adrenalin.

Brain

Normally, Cortisol concentrations do not change with ageing [128]. According to Stawski [129], cognitive function in his study with 1500 humans ranging between 33 and 84 years was associated with sound cortisol profiles, including a steeper diurnal cortisol rhythm, higher morning and lower evening levels.

In healthy older men, higher plasma cortisol levels were negatively associated with ageing-related overall cognitive function (memory and processing speed) but not ageing-related brain atrophy [130]. Porter [131], observed, that effects of corticoids on cognitive brain function do not occur only after disrupting the diurnal rhythm of cortisol by a high dose of cortisol (10 fold elevation). In addition, Lupien [132] showed that subjects presenting a decrease in cortisol levels with years performed as well as young healthy subjects with regard to cognitive performance. Thus, impaired cognitive performance was associated with recent evidence of hypothalamic-pituitary-adrenal dysregulation and elevated basal cortisol levels.

Elevated cortisol

In general, it is reported that corticosteroids impair selective attention, that is, the ability to discriminate relevant from irrelevant information, which is in accordance with electrophysiological findings that acute administration of cortisol to human subjects reduces the average evoked potential response to relevant but not to irrelevant stimuli [133]. These findings are also consistent with studies showing that glucocorticoids can impair and hippocampal long term function [134].

The role of the hippocampal formation in human learning and memory is now well established [135]. More importantly, studies report that the hippocampus is essential for the long term memory [136], which is necessary conscious or voluntary recollection of stored information.

In addition to cognitive impairment, elevated cortisol presents numerous side effects such as [137]:

- Skin: skin atrophy, disturbed wound healing

- Skeleton, muscle: osteoporosis, muscle atrophy, myopathy

- Eye: cataract, glaucoma

- CNS: mood swings, euphoria, depression, suicide attempts, mania, hallucinations, and delusions

- Endocrine systems: diabetes mellitus, adrenal insufficiency

- Cardiovascular system: hypertension, dyslipidemia, a reduced fibrinolytic potential

- Gastrointestinal system: peptic ulcers, upper gastrointestinal bleeding, pancreatitis, oral candidiasis

- Immune system: increase of all kinds of infections, inhibition of the inflammatory and specific immune systems, reactivation of cytomegalovirus

- skin atrophy, disturbed wound healing

- diabetes mellitus

- adrenal insufficiency.

Conclusions

While cortisol-induced additional glucose would certainly delay onset of fatigue in physical and mental strain, some special effects of corticosteroids on brain will impair chess performance. It must be realized from these data that significant elevations of cortisol for longer periods cause hippocampal dysfunction and cognitive impairments in long time memory, which would directly affect the competitive chess player. If a certain threshold of hippocampal dysfunction is reached, it can be postulated that neuron loss will occur that will be related to more severe and irreversible cognitive deficits (Table 3).

Drugs for improvement of mental performance in chess

Mental performance consists of several cognitive functions which are distinct but very coherent. Memory is the ability to remember learned materials or events. Attention is the ability to focus while ignoring distractions. Creativity is the ability, to establish new relationships and new non-obvious meanings. Intelligence is the problem solving ability [138].

An expert chess performance is based on a specific domain expertise consisting of above described properties of mental performance. The expertise is obtained by

- At least ten years of training

- Beginning as early as possible in life

- Spending at least 10000 hours training time in those ten years

- Memorising up to 10000 chess positions at master level and 300000 at grand-master level [139,140].

Can drugs really accelerate the process of obtaining chess expertise? Can a grandmaster participating in a tournament really improve his actual chess expertise gained in 20 years of continuous training and participating in thousands of competitive chess games by taking drugs before the actual tournament? Should a chess player take cognitive drugs from the beginning of chess training (in the ideal case already before beginning of elementary school) in order to become a superior chess master many years later?

Neurological basis of mental expertise in chess

Expertise in a specific mental domain such as chess enables a chess player to perform as an expert is an intrinsically cognitive domain which taps many cognitive processes that are typically associated with intelligence, such as mental speed, spatial abilities, working memory, reasoning and perception [141,142], motivation [143], attention [144], recognition [145] and creativity [138].

Summary of desired effects and side effects of drugs for CE

Lanni summarized mental performance with memory, attention, creativity and intelligence [138]. These cognitive functions also are also essential parts of chess expertise. Lanni [138] assigns in his review diverse CE drugs to attention, memory and creativity (Table 4) in diverse clinical settings, but not one to intelligence. Intelligence is a difficult term in Biology and Psychology. For example, the intelligence quotient (IQ) of experienced chess players is not significantly different from that of the general population [146,147]. Obviously, a long and intensive chess training of experienced chess players could not enhance intelligence as measured by IQ-tests. For this reason Grabner [140] defined for chess players a domain specific intelligence for very good chess players. In consequence a similar mental expertise (specialized domain specific intelligence) will be found also as musical intelligence, logical-mathematical intelligence, spatial and visual intelligence, linguistic intelligence, physical-kinaesthetic intelligence, interpersonal or "social" intelligence, intrapersonal or intuitive intelligence, balanced intelligence and so on [148].

CE drugs were originally developed to treat cognitive disabilities such as narcolepsy, dementia, AD, PD, schizophrenia or ADHD and depression [16].

Increasingly, however, healthy individuals use CE drugs such as moldafinil and methylphenidate to improve cognitive functions including attention and working memory [16,149], On university campuses around the world, students are striking deals to buy and sell prescription drugs such as Adderall and Ritalin - not to get high, but to get higher grades, to provide an edge over their fellow students or to increase in some measurable way their capacity for learning, as if traditional use of substances to enhance cognitive and psychomotor performance such as caffeine and nicotine seem insufficient to counteract the consequences of our 24 hour society. For example, in a study of the University at Mainz, Germany, the estimated 12-month prevalence of CE drug use among the students was 20%. Prevalence varied by sex (male 23.7%, female 17.0%), field of study (highest in students studying sports-related fields, 25.4%), and semester (first semester 24.3%, beyond first semester 16.7%) [150].

A thorough search of the scientific literature on CE drugs, however, creates no optimism on efficacy of CE drugs at the moment. When rigorous standards for clinical studies are applied (placebo controlled, double blind, magnitude of effects and side effects), only a few studies remain for evaluation of efficacy of CE-drugs.

Despite wide-spread optimism, available pharmacological agents do not seem to provide substantial cognitive-enhancing effects [151].

There exists till now no robust evidence that these agents have a particular and appreciable advantage in terms of improving cognitive functioning. Even though studies find statistically significant treatment effects on cognition, these gains are poor or almost impalpable on a clinical and functional level. Furthermore, there exists no information on the long-term effects on cognition. In addition, the studies show

Hormone	Glucose/ Glycogen	Mental performance		General side effects
		Normal concentration	**Elevated concentration**	**Elevated concentration**
Epo	No effect	No effect[1]	No effect[1]	Cerebral seizures, hematomas and haemorrhages, stroke, hypertension, cardiovascular risks vascular access, thrombosis risks, occurrence of death
GH	No effect	Positive effect	Negative effect	Acromegaly, insulin resistance, hyperglycemia, hyperinsulinemia, hypertension, decreased glucose utilization, increased lipoplysis, leukemia, hypothyroidism, increased mortality in critically ill
IGF-I	Positive effect	Positive effect	Negative effect	Muscle hypertrophy, muscle mitogenic, increase of premenopausal breast and prostate cancer
LH/hCG	No effect	No effect	Negative effect	Hypogonadism
Insulin	Positive effect	Positive effect	Negative effect	Hypoglycaemia, sometimes with severe brain dysfunction and seldom death, mood changes, depression, anxiety
ACTH (cortisol)	Positive effect	No effect	Negative effect	Decline mental performance, diseases of skin, skeleton, muscle, eyes, CNS, endocrine systems, cardiovascular system, gastrointestinal system, immune system
AAS	No effect	Positive effect	Negative effect	Cardiovascular, arteriosclerosis, cardiomyopathy, decrease of visiosapatiol memory, pattern recognition
Anabolic agents Clenbuterol	No effect	-	Positive effects for low baseline	Cardiac toxicity and type II MI with associated symptoms such as agitation, palpitations, tachycardia, hypokalemia, and hyperglycemia
Ampheta-mines	No effect	-	Positive with limited significance	Cognitive impairments, multiple deleterious medical consequences, including paranoia mimicking full-blown psychosis, hypertensive crisis leading to stroke
Caffeine	No effect	-	Positive effect	Aortic stiffness, increased vascular resistance, decreased cerebral blood flow, increased plasma epinephrine, lipids, and renin. increased risk of cardiotoxicity, including MI and sudden cardiac death
Nicotine		-	No effect In elderly negative effect in normal	Sudden death can be caused by cardiovascular arrest, respiratory muscle paralysis and/or central respiratory failure.
Narcotics (cocaine)	No effect	-	Negative effect	Cardiotoxicity, ventricular arrhythmia, systemic hypertension, acute MI, ventricular hypertrophy. Coronary artery disease, mortality is four eight times higher than in the general population.
CE-drugs		-	Positive for low base line of cognition, with limited significance for normal cognition	Many deleterious side effects, including toxicity with danger of life and physical or psychological dependence

[1]Positive effect only at high altitude or with lung disease.

Table 3: Summary of effects of AAS, AS, nicotine, narcotics and hormones on chess performance.

that there are little differences in terms of cognitive-enhancement even compared to placebo: one study [152] even showed a better cognitive improvement in the placebo group. In addition, many of the CE drugs are most effective only on patients characterized by the lowest baseline of cognitive performance [153-157], while even impairing performance of patients with high baseline cognitive function [154,158-161].

For the time being, available pharmacological agents seem to provide modest (if any) appreciable cognitive benefits to patients suffering cognitive deficits. Furthermore, there seems to be rather scarce evidence of any direct specific cognitive-enhancing effect of drugs on normal persons, such as chess players.

Alternatives for use of CE-Drugs

In respect to the efficacy of CE drugs, it seems reasonable to hypothesize that more resources - both financial and human - might be better off invested in complementary treatment schemes (e.g., cognitive remediation, vocational training, metacognitive training) that do provide important, direct, and meaningful improvements for patients and normal persons.

Indeed, a number of approaches to remediating cognition in

schizophrenia have been developed and studied in the last 15 years and this literature has been reviewed in six meta-analytic studies. With the exception of one [162], all have found moderate to large effect sizes [163-167] effect sizes far greater than those observed for any drug treatment. Also, these remediation effects are durable up to at least 6 months after the interventions are withdrawn [168]. Finally, and most importantly, these neuropsychological gains translate to improvements in real-world activities [169-171]. Similarly, cognitive remediation programmes address prominent, complementary functional domains such as social cognition - and studies have furthermore observed beneficial effects on functional outcome measures in patient's post-treatment [172,173]. Future studies should furthermore address the combination of cognitive and pharmacological treatment schemes that provide the widest and more enduring benefits for the patients.

The downside of drugs for CE

Many of the CE drugs may be accompanied by deleterious side effects, including toxicity and physical or psychological dependence. These risks may be exacerbated by long-term use, which may be necessary to achieve or maintain the desired enhancement effect.

Like all drugs, those used with the aim of enhancing cognition

can have side effects via body systems other than the brain. Thus, both Acetylchilinesterase-Inhibitors (AchEIs) and methylphenidate frequently cause gastrointestinal upset or nausea, sometimes leading patients to discontinue medication altogether. Adderall, for example, a combination medication (amphetamine and dextroamphetamine) is widely used in the USA to treat ADHD as part of a total treatment plan, including psychological, social, and other treatments. It may help to increase the ability to pay attention, concentrate, stay focused, and stop fidgeting. Adderall has numerous side effects ranging in the alphabet from appetite loss to sudden death.

These effects have the potential to offset any positive effects of the drug on overall performance, and also need to be borne in mind by anyone contemplating use of such drugs for non-medicinal purposes. More important from a cognitive neuroscience perspective is the ability of some drugs to impair certain aspects of cognition while simultaneously enhancing others in the same individual.

Thus, rivastigmine in healthy elderly subjects can improve learning on a motor task and making associations between symbols and digits, but can at the same time impair verbal and visual episodic memory [174]. Similarly, the dopamine agonist bromocriptine can enhance spatial Working Memory (WM) while simultaneously impairing probabilistic reversal learning in young participants [175]. This finding echoes results in patients with PD: dopaminergic medication improves their performance on WM and task-set switching tasks, but degrades reversal learning [176]. It has been hypothesized that such opposing effects are due to 'overdosing' of ventral striatal areas involved in the latter, but replenishment of dopamine in dorsal striatal areas required for the former [177]. Thus, doses of dopaminergic medication sufficient to ameliorate motor function and some aspects of cognition in PD have the potential to worsen others.

Indeed, this conclusion might well be applicable to recent reports that some PD patients on dopaminergic agonists developed impulsive behaviors such as gambling, compulsive shopping and hypersexuality [178,179]. It has been reported that such behavior in PD is often associated with the presence of dyskinesia, involuntary movements due to excessive dopaminergic stimulation [180], consistent with the notion that such impulse control disorders might indeed be associated with 'overdosing' of some basal ganglia regions. Importantly, reducing the dose of dopaminergic drugs often leads to reductions in impulsivity. These findings show that dopamine agonists in PD can have a spectrum of effects, both beneficial and harmful, on cognition and behavior.

Effects of Genotype on Drug Response

Genetic predictors of individual variability in response to treatments aimed at improving cognitive function would clearly be beneficial in effective targeting of therapeutic strategies. Several studies have suggested a role for polymorphisms in the catechol-O-methyltransferase (COMT) enzyme-coding region on chromosone 22 in WM. COMT degrades catecholamines, including dopamine, at the synapse. Polymorphisms of the COMT gene seem to be associated with variability in human WM performance and associated brain activity, presumed to be via its putative influence on cortical dopamine levels [181].

For the AChEIs, extensive metabolizers of drugs as defined by gene variations in cytochrome P450 (a family of degradative enzymes) might show greater response to donepezil and rivastigmine [182,183].

Conclusion

It is fair to say that we are still in the first generations of studies to examine the potential for CE in humans. In both healthy individuals and many patient groups, the overall effects of drugs generally seem to be modest. However, there is evidence that there might be more significant effects in subgroups, such as those whose baseline performance is poorest or individuals with a particular genotype.

Chess players, especially those who compete competitively are usually characterized as persons with a cognitive performance in their specific domain ranging far away from baseline cognition, where CE drugs are sometimes effective, mostly without clinical significance. It is not conceivable, that the CE dugs of today will enhance chess expertise.

In addition, the described side effects of CE drugs have the potential to offset any positive, if here is one, effects of the drug on overall performance, and also need to be borne in mind by anyone contemplating use of such drugs for non-medicinal purposes.

Class	Drug	Cognitive domain	Approved use	Off label or investigational use
Cholinergic agents	Donezepil, rivastigmine, galantamine	Memory, attention	Symptomatic treatment of AD	Vascular dementia, dementia associated with PD, with memantine to improve attention/executive function in AD patients, Down patients, may improve core ADHD symptoms, used in militare personnel to treat psychic trauma.
Nicotinic agents	Nicotinic alpha-7 receptor agonists (MEM 63908, MEM 3454) Memory – MEM 63908 for AD; MEM 3454 for schizophrenia and/or AD Alpha4beta2 nicotine, Acetylcholine receptor partial agonist (TC-1734)	Memory	None None	MEM 63908 for AD; MEM 3454 for schizophrenia and/or AD AD, cognitive deficits in schizophrenia and other conditions marked by cognitive impairment such as ADHD; AAMI; and MCI
Glutamatergic agents	Ampakine	Memory, attention	Treatment of patients with moderate to severe AD	CX516 for cognitive deficits in schizophrenia
	Memantine	Memory, attention		Chronic headache and migraine prevention; treatment of ADHD in paediatrics patients; in association with rivastigmine to improve the attention/executive function in AD patients

Agents once supposed to act through glutama-tergic mechanisms	Piracetam	Memory, attention	Used in attention and memory disorders of degenerative or vascular origin in the lderly,treatment for alcohol withdrawal.	Potentially used for AD and MCI
	Aniracetam		Used in attention and memory disorders of degenerative or vascular origin in the elderly	Potential treatment for cognitive impairment associated with AD and schizophrenia, depression, slowing the progression and potentially enhancing recovery from PD.
	Oxiracetam		Used in attention and memory disorders of degenerative or vascular origin in the elderly.	Potentially used for AD and MCI
	Nefiracetam			Although it is not conclusively shown to be effective as an AD medication, it could possibly be useful as an analgesic
Stimulants and agents active on catecholamines	Methyphenidate	Memory, attention	Treatment for ADHD and narcolepsy	Used to improve attention in students
	Moldafinil		Narcolepsy; approved for use in the US and certain European countries in patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnoea/hypopnoea syndrome or shift-work sleep disorder; in some countries, it is also approved for idiopathic hypersomnia.	Used to suppress the need for sleep, to contrast general fatigue unrelated to lack of sleep (see for example the administration to healthy military personnel), to treat ADHD, and as an adjunct to antidepressants (Particularly in individuals with significant residual fatigue).
	Atomoxetine		Treatment for paediatric and adult ADHD	Quite diffused in healthy students to enhance attention
Agents that act on cerebral circulation/ metabolism	Nimomidine	Memory	Approved for oral administration to improve neurological outcome after subarachnoid hemorrhage.	
	Idebenone			Treatment for Friedreich's ataxia and stroke
	Hydergine, nicergoline		Used in brain disorders of vascular origin in the elderly	Used to combat decreased mental function as a result of senility or multiple small strokes
Antidepressant (NASSA)	Mirtazapine	Attention	Used for the treatment of moderate to severe depression or as an add on medication to enhance the effectiveness of agents such as duloxetine and venlafaxine in severe and treatment-resistant depression.	Used to contrast panic disorder, generalized anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder
Miscellaneous others	Acetyl-l-carnitine, lecithin, gingko biloba, ginseng, antioxidants	Memory, attention	Some of them may have approved uses in EU countries for various conditions. Widely used in integrator formulations to improve mental performance	Supplementation has been shown to be neuroprotective in cerebral ischemia, peripheral nerve injury and to reverse symptoms associated with mental decline in the elderly. Studied in Alzheimer's disease and other dementias. Can improve attention in healthy individuals and improve cognitive performance in various neurodegenerative disorders.
Cannabis derivatives	Marijuana	Creativity	None	Used to reduce chronic pain, to treat pain caused by rheumatoid arthritis, to relieve spasticity in multiple sclerosis, to treat epilepsy owing to its serotonin-mediated anticonvulsant action.
Psychomimetics	Lysergic acid diethylamide (LSD), psilocybin		None	Treatment of cluster headache and of patients with personality disorders, affective disorders and adjustment disorders, and used to reduce anxiety and pain in cancer patients.

The table does not list the variety of integrator's cocktails that are advertised in Internet as memory boosters. Abbreviations-AD: Alzheimer's disease; PD: Parkinson's disease; MCI: mild cognitive impairment;
AAMI: age-associated memory impairment. Numbers with MEM, CX or TC for special pharmaceuticals.

Table 4: Drugs for cognitive enhancement [138].

Instead, a complementary treatment schemes (e.g., CE by chess training with chess boards, chess books, building chess images, visual observation of chess games, vocational training with chess, metacognitive training, and additionally regular light physical stress) that would provide important, direct, and meaningful improvements for chess players cognition and maintain any level chess expertise (Table 4).

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